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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,605	05/31/2002	Ulrike Fiedler	1406/37	8368

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EXAMINER	
BORIN, MICHAEL L	
ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/030,605	FIEDLER ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-12,14-18 and 20-46* is/are pending in the application.

4a) Of the above claim(s) *17-25,29-41 and 43-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-12,14-16,26-28,42,46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/12/2006 has been entered.

Status of Claims

1. Claims 3,4 are canceled. Claims 1,5-12,14-18,20-46 are pending. Claims 17, 18-25,29-41,43-45 remain withdrawn from consideration. Claims 1,5-12,14-16,26-28,42,46 are under consideration to the extent they read on the elected species.

2. Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1,5-12,14-16,26-28,42, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

A. Claims 1, 42 fail to particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant . From one hand, the claims state that amino acids to be mutagenized are located "in at least two β-strands". From another hand the same claims state that that amino acids to be mutagenized are located "in two, three or four β-strands"

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1,42 recite the broad recitation of "at least two β-strands", and the claims also recite "two, three or four

β-strands" which is the narrower statement of the range/limitation. Note that the limitation "at least two β-strands" is removed from the amended claim 46.

B. Claims 1,42,46 (and claims dependent thereupon): the term "antibody-like binding activity" is not clear. The specification mentions that "binding properties means, for example the specific activity of an antigen to an antibody" (p. 12, 2nd paragraph). This, however, does not define the meaning and the scope of the term "antibody-like binding activity". It is not clear what range of binding activity is encompassed by the "antibody-like binding activity"; it is not clear whether the "antibody-like" binding activity means similar affinity or similar avidity (i.e., mutant's affinity of multiple antibody - antigen interactions when more than one takes place between the two molecules). Or does it mean that "antibody-like binding activity" means similar functional effect of binding, such as neutralization or agglomeration? The specification, although providing particular examples, does not provide a standard for ascertaining the meaning of the term, and one of ordinary skills in the art would not be reasonably appraised of the scope of the invention.

Also, it is noticed that the claims use two different terms with respect to "antibody-like": "Binding activity" – as in the beginning at end of claim 1, for example, and "binding specificity" – as in claim 1(i), line 5, or claims 14,15, for example. Please clarify.

Claim Rejections - 35 USC § 112, first paragraph (enablement).

The following rejection is modified in view of applicant's comments and amendments to the claims.

4. Claims 1,5-11,16,26-28,42,46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mutants of bovine gamma crystallin of SEQ ID No. 22 obtained by mutations at positions identified in claim 12, does not reasonably provide enablement for mutants of other crystallins, much less for other proteins with mutations at beta sheet structure as claimed.

The breadth of the claims encompasses any polypeptide selected from those listed in claims 1, 46 (or, more narrowly, any gamma-crystalline polypeptide as in claim 42) comprising beta sheet and mutated at any residue located in at least two beta strands of at least one beta sheet such that the mutant possesses "antibody-like" binding towards a pre-selected binding partner. Specification states that it is possible to mutagenize virtually all proteins which display beta-sheet structures (p. 8, 2nd paragraph).

Specification exemplifies the invention by disclosing mutants of gamma-II-crystalline of SEQ ID No. 22. Specification teaches that the initial protein, gamma-II-crystalline "has no binding properties whatsoever" (p. 4, second paragraph). For this protein, eight particular residues located in three beta strands on the surface were selected and randomized by site-specific mutagenesis. Out of 26 billion (!) mutants generated (p. 13, last paragraph) only one "expected amino acid exchanges" is discovered (p. 13, third full paragraph). Seven residues K3,T5,Y7,C16,E18,S20, and

D39 have the same mutation to R3,K5,K7,Y16,S18,N20, and L39 in the two mutants obtained, SEQ ID No. 19 and 21. Except for gamma-II-crystalline SEQ ID No. 22, specification does not provide any working examples of any other mutants of crystallins mutated at any other residues than the residues indicated for SEQ ID No. 22.

Except for being located in β strands on the surface of the protein, no guidance is provided for selecting a number and/or location of residues to be mutated. The eight residues selected for mutation are described as forming "a continuous surface segment" which happened to be located in three beta strands (Sheme B), no guidance is offered of selecting particular residues from those located in "at least two beta strands" as claimed. Further, the mutants of the invention, as now claimed, have functional limitation of having new or improved antigen binding specificity towards a binding partner. Specification does not provide guidance on how to select residues suitable for mutagenesis to yield a mutant with "antibody-like" binding activity towards a particular partner of interest.

For comparison, in a similar method of creating mutant antibody-like proteins derived from lipocalin, Beste et al, first developed a set of criteria to identify residues suitable for random mutagenesis to achieve binding to a non-natural ligand: location in natural ligand-binding pocket, ability to contact a natural ligand, and non-interference with residues forming hydrophobic core. No such guidance is offered with respect to mutants as instantly claimed.

It is well known in the art that it is difficult to predict the functional effects of random single amino acid substitutions, and nearly impossible to predict the functional effects of multiple amino acid substitutions. The relationship between the sequence of a peptide and its tertiary structure (and thus its binding activity) are not well understood and are not predictable (see Ngo et al.).

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make the invention with the claimed breadth without an undue amount of experimentation.

Claim Rejections - 35 USC 112, first paragraph (written description).

Upon consideration of the amended claims and the specifcation, it was deemed necessary to re-introduce the written description rejection, first applied in the Office action mailed 08/10/2005. The rejection is revised as follows.

5. (Written Description) Claims 1,5-11,16,26-28,42,46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The breadth of the claims encompasses any polypeptide selected from those listed in claims 1, 46 (or, more narrowly, any gamma-crystalline polypeptide as in claim 42) comprising beta sheet and mutated at any residue located in at least two beta strands of at least one beta sheet such that the mutant possesses "antibody-like" binding towards a pre-selected binding partner. Specification states that it is possible to mutagenize virtually all proteins which display beta-sheet structures (p. 8, 2nd paragraph).

The claimed genus of mutant proteins selected from those listed in claims 1, 46 is represented by two mutants of gamma-II-crystalline of SEQ ID No. 22 having seven residue-mutation of residues K3,T5,Y7,C16,E18,S20, and D39 into R3,K5,K7,Y16,S18,N20, and L39. These mutants, having very particular substitutions, are not sufficiently representative of the genus of any mutants of proteins listed in claims 1; they are not sufficient to reasonably convey to one skilled in the relevant art that the inventors had possession of the entire genus of the mutants as claimed.

Further, the claimed mutants are addressed as having a functional limitation of having "antibody-like" binding activity towards a binding partner. The only binding partner disclosed for the mutants addressed above is BSA-estradiol-17-hemisuccinate. The generally stated functional limitation of having "antibody-like" binding activity towards any binding partner does not provide sufficient structural characteristics to define the genus of the claimed proteins. Note, that the claims are directed to products, not to a method of making.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that besides one very specific mutant containing mutations at seven particular locations of bovine gamma II crystallin and having binding affinity for particular binding agent, BSA-estradiol-17-hemisuccinate, applicants generated any other crystalline protein having new characteristics other than ability to bind BSA-estradiol-17-hemisuccinate. Much less there is any demonstration in the specification of any other protein which, being mutagenized, appropriated new functional characteristics as claimed.

Prior art made of record

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Koide et al (US 6,673,901) teaches monobodies (mutants with antibody-like binding properties) generated from fibronectin type III. The reference is not being applied as crystallins are elected species.

7. Claims 12,15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and rewritten to overcome the rejection under 35 U.S.C. § 112 .

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571)272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb